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Relationship between causes of aberrant methylation in Acute Myeloid Leukemia and the resulting methylation profiles

With an estimated 21,380 cases in 2017, Acute Myeloid Leukemia accounted for 1.3% of all new cancer cases and was the cause of 10,590 deaths, accounting for 1.8% of cancer-related deaths. [[1]](#footnote-1) While patients with AML generally have fewer genetic mutations than patients with other cancers, epigenetic modifications, primarily DNA methylation, has been implicated as a major driver in the development of de novo cases[[2]](#footnote-2) and the level of methylation/epigenetic differences is often used in prognosis development.[[3]](#footnote-3) While many differentially methylated regions (DMRs) have been found in patients with AML as opposed to healthy patients, no study has focused on the differences in methylation profiles between known oncogenes in AML and other, unrelated genes. Additionally, there is a need to understand whether the specific genomic mutation present in a patient with AML will dictate distinct patterns of aberrant methylation in the patient.

Understanding the effects of aberrant methylation in AML and potential intervention pathways continues to hold promise for the future of treatment of AML. The objective of this study is to determine whether factors such as genomic mutation status result in similar changes in the methylation status of known AML/cancer genes. My hypothesis, based on information gathered from previous studies that have shown that genes implicated in aberrant methylation result in different effects on methylation at a genome-wide level, is that the aberrant methylation present in known oncogenes in AML and other cancers is likely affected similarly across samples with similar genomic mutations to known methylation genes (DNMT3A, IDH1/2, TET2, WT1). My goal is to investigate this relationship with The Cancer Genome Atlas (TCGA) AML dataset to establish whether a relationship exists between the genomic cause of aberrant methylation and the resulting methylation profile. This knowledge will allow us to contribute observed methylation changes in AML patients to known causes, elucidating potential divergences from expected effects in further studies.

**Aim 1:** **Collect, perform normalization methods, and annotate the TCGA data with genomic region information.** Assembly and normalization of the data will be conducted by using pipelines developed within the *Bioconductor* community including normalization packages (such as *watermelon* and *lumi*) specifically built for methylation array data. The resulting dataset will be analysis ready and methods documented for future analyses of similar data.

**Aim 2:** **Analyze the observed methylation changes of AML-implicated and other oncogenes for consistency with respect to factors such as genomic mutation status.** Differential methylation analysis will be performed on regions of the genome associated with AML and other cancers, including distal regions such as promoters and enhancers, to determine whether shared factors such as mutation status result in similar profiles across samples. This knowledge will allow us to attribute observed changes in methylation status to potential causes so that inconsistent observations may be primarily focused on.

The proposed study will take a focused view into the methylation changes observed in oncogenes in patients with AML and stratify based on factors such as genomic mutation status. The expected result of this study is to determine whether factors such as genomic mutation status can be used to attribute methylation changes in patients with AML to specific causes. This will allow future researchers to prioritize observations which deviate from the previously studied patterns, potentially elucidating a new path to further understanding the disease.

1. https://seer.cancer.gov/statfacts/html/amyl.html [↑](#footnote-ref-1)
2. http://www.nejm.org/doi/full/10.1056/NEJMoa1301689 [↑](#footnote-ref-2)
3. http://www.pnas.org/content/114/28/7414 [↑](#footnote-ref-3)